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ISTITUTO DI GENETICA
UNIVERSITÀ DI PAVIA
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Dear Joshua,

I have been to Paris for a short Symposium, and am answering only now your letters, among them the note of June 15.

1) Both Giovanni and I would be very happy to see you if you can make it. Should it be impossible for you to come now, Giovanni plans to visit you in October or November, either in California or after the Macy's conference on the East Coast. Alba and I are likely to be atSanta Margherita at that time, i.e. most of August, and leaving for Israel (Symposium on Human population Genetics) on or around 27th August. If you want to spend some days on the seaside at the end of August the crowd is not too bad. It is not likely unfortunately that we may have room for you at home, but there should be no difficulty in booking room at a hotel. I could easily collect you at Milan airport, and deliver you there again. End of August is usually not too hot. Giovanni will be near Viareggio and could join easily at Santa Margherita, so we could have an Interist meeting on the beach.

2) Interist. We have not been too active until now, among other reasons because we did not know with certainty about renewal. Verbal confirmation of renewal has now come, twice and an official letter should arrive soon. When such a letter of Interist will be in our hands we shall send you an official letter renewing our agreement. We shall be in a position to renew it from beginning of 1962 to end of 1965.

We have discussed recently our programs for next (academic) year and we feel inclined towards the following lines. Naturally we would be happy to discuss all of them with you if we see you in the Summer.

a) Nice Project (fluorine). The chemist Rossi is here after a period of training on antibiotic purification at Lepetit and has started preparing chemically yeast autolysate for fluorination (i. e. : epoxidation with alkaline H_2O_2, per-phtalic acid; treatment with periodic acid; chlorination with PCl_5). This was done some time ago already but fluorination did not take place afterwards, and we prefer to work on fresh solutions. This is being done on yeast extract and will be done on bacterial extracts: on the latter we will also try nitrous acid.

b) Penicillanic acid. Since Giovanni's discussion with you at Princeton, we have reconsidered the matter. It seems a random screening is not likely to be very profitable. Bristol, Lepetit, and Beecham have explored thousands of conjugations and none has worked sofar, at least in giving both acid and enzyme resistance. Moreover, a test for acid resistance on impure products is dangerous; we have been duped by it. If you are interested in having literature on the subject, we could let you have it. Before we undertake anything we would like to rediscuss with you if it is worth the trouble.

c) DAP analogues: another trial to induce the Lepetit chemists to do something about it will perhaps be successful. They should prepare bromine and fluorine derivates, if the difficulties are not too great.

d) Genetics of actinomycetes. All trials to reproduce transformation have been unsuccessful, but we will try again next year.
" Recombination " has been obtained in S. rimosus and in S. aureofaciens but not between the two. It seems it is not heterokaryosis but it will take more time and markers to be sure about it. Transduction will be tried on S. mediterranei, where we have some four or five good phages, one of them giving what look turbid plaques. This actinomycete is used for the production of rifomycin (which will be marketed soon by Lepetit and Schering).

e) A B. subtilis strain made resistant to 800 γ/ml of terramycin, and sensitive to 30-40 γ/ml of all other tetracydines is being used to test X-ray and UV induced mutants of S. rimosus. The screening has just been started.

f) It is also being tested if extracts of S. rimosus can hydroxy late tetracycline, and extracts of S. aureofaciens can chlorinate it. Should any of the two succeed, it might be possible to produce oxychlorotetracicline, etc.

Re Alikhanian: we have been in communication with him, asking him strains by letter: but he did not answer. We saw a transduc tion paper on Nature but would like if possible to have the tran slation of the Russian paper, if you can let us have it.

These are the programmes under way now; we expect ~~the~~ chance of discussing them with you.

3) Orio Ciferri thanks you for the ADP analogue. He will have to purify the enzymes first.

4) Could I have exact indications of the silicagel you use for den sity gradients wich might also be employed for solid medium plates?

5) I am enclosing a note on the treatment of the hemophilia problem.

6) I have started writing a booklet of human genetics but it is perhaps a little too elementary. I will send you the plan of it: I have started writing it in Italian. I should very much appreciate your opinion. I have a half word of Ruggero who would like to join in it, but it would seem incredibly ingenuous on my side to give ~~to~~ serious credit to it. Any collaboration I could have from you, of whatever degree, would be highly appreciated.

Maybe we shall see you soon? All the best, and thanks for the jumbo from Colorado.

Yours,

L.L. Cavalli-Sforza

Hemophilia problem.

I usually prefer the Bayesian approach, because it is the most general. This is what I call the following, which is probably what you call contingent probabilities:

If there are several possible alternative ways, a, b, c, . . . in which an event may occur, and

$\pi_a \quad \pi_b \quad \pi_c, \ldots .$ $\qquad\qquad \Sigma \pi_i = 1$

are the (a priori) probabilities that a, b, or c, . . . take place;

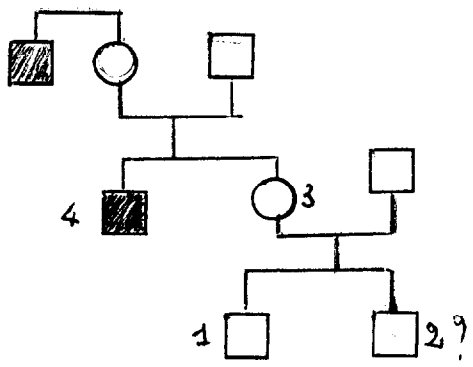
$p_a, \ p_b, \ p_c, \ldots .$

are the probabilities that if a, b, or c have taken place, one (or more) given observed events occur, then:

$$P_a = \pi_a p_a / \Sigma \pi_i p_i$$

is the (a posteriori) probability that the observed events have occurred due to "cause" a etc.

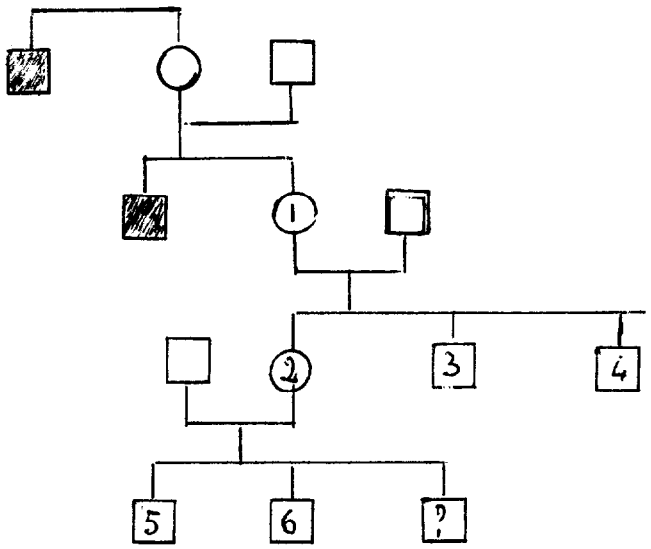
In your case:



the observed events are that 1 is normal, 4 hemophiliac (and his maternal uncle a hemophiliac, to rule out fresh mutation).

f_a that 3 is HH is 2/3, and $1-f_a$ that it is Hh is 1/3, hence $P_2 = 1/6$. Your shortest through nephewships is of course correct.

It may become more complicated in a case like this:



Here there are three possibilities, a, b, c, and the observed events are that 3, 4, 5, 6 are normal.

	1	2	π	Probab. of 3, 4, 5, 6 normal	Product
a	het	het	1/4	1/16	1/64
b	het	homo	1/4	1/4	1/16
c	homo	homo	1/2	1	1/2
					37/64

Probab. that 2 is het: $\frac{1}{64} \Big/ \frac{37}{64} = \frac{1}{37}$

Probab. that ? is hemophiliac 1/74